REMARKS

Reconsideration and withdrawal of the rejections of the application respectfully requested in view of the amendments, remarks and enclosures herewith, which place the application in condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 84-118 are pending in this application. Claim 118 has been clarified to depend from claim 84 or 85. No new matter has been added.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited in the Office Action, and that these claims were in full compliance with the requirements of 35 U.S.C. § 112. The amendments of the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

II. THE DOUBLE-PATENTING REJECTIONS ARE OVERCOME

Claims 84, 85, 96 and 116-118 remain rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of U.S. Patent No. 6,376,473 ("the '473 patent") in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999). Claims 84-91 remain rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of the '473 patent in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Xiang et al. (Immunity 1995, 2:129-135), and Baker et al. (US Patent 5,106,733). Claims 84, 92, 94, 95, 100 and 108 remain rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of the '473 patent in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Li (WO 96/40945). Claims 84, 93, 97, 98 and 104 remain rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of the '473 patent in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Choi et al. (Virology 1998, 250:230-240). Claims 84-118 remain rejected under the judicially created

doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of the '473 patent in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Xiang et al. (Immunity 1995, 2:129-135), Baker et al. (US Patent 5,106,733), Li (WO 96/40945) and Choi et al. (Virology 1998, 250:230-240).

Claims 84, 85, 96 and 116-118 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of the '473 patent in view of U.S. Patent No. 6,586,409 B1 ("the '409 patent"). Claims 84-91 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of the '473 patent in view of the '409 patent and further in view of Xiang et al. (Immunity 1995, 2:129-135), and Baker et al. (US Patent 5,106,733). Claims 84, 92, 94, 95, 100 and 108 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of the '473 patent in view of the '409 patent and further in view of Li (WO 96/40945). Claims 84, 93, 97, 98 and 104 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of the '473 patent in view of the '409 patent and further in view of Choi et al. (Virology 1998, 250:230-240). Claims 84-118 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of the '473 patent in view of the '409 patent and further in view of Xiang et al. (Immunity 1995, 2:129-135), Baker et al. (US Patent 5,106,733), Li (WO 96/40945) and Choi et al. (Virology 1998, 250:230-240).

Claims 84, 85, 96 and 116-118 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of the '473 patent in view of the '409 patent. Claims 84-91 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 5-8 of the '473 patent in view of the '409 patent and further in view of Xiang et al. (Immunity 1995, 2:129-135) and Baker et al. (US Patent 5,106,733).

These rejections are addressed collectively and are respectfully traversed.

The issue of whether there is indeed double patenting is contingent upon whether the remarks herewith are indeed considered and entered; and, if so, whether the Examiner believes there is overlap with claims ultimately allowed in the application. If, upon agreement as to

allowable subject matter, it is believed that there is still a double patenting issue, a Terminal Disclaimer as to the '473 patent will be filed for the purposes of expediting prosecution.

Accordingly, reconsideration and withdrawal of the double patenting rejection, or at least holding it in abeyance until agreement is reached as to allowable subject matter, is respectfully requested.

Applicants respectfully request that the Examiner consider PCT Publication No. WO 98/03200, which was filed as Serial No. PCT/FR97/01325 on July 15, 1997. The PCT Publication was cited in the Supplemental Information Disclosure Statement filed November 3, 2004, and the Examiner made of record in the Office Action. The '473 patent is a continuation-in-part of International Application Serial No. PCT/FR97/01325 (the '01325 application). Applicants respectfully submit that the text of the '473 patent encompasses the text of the '01325 application.

There is no teaching or suggestion in the '473 patent to combine a DNA vaccine with a cationic lipid containing a quaternary ammonium salt and having the indicated formula. Furthermore, the Office Action admits that the '473 patent does not teach that the vaccine comprises a cationic lipid. However, the Office Action alleges that it would have been obvious to combine the '473 patent with Klavinskis et al. or the '409 patent.

Applicants remind the Examiner that it is impermissible to engage in a hindsight reconstruction of the claimed invention, using the Applicant's structure as a template, and selecting elements from references to fill in the gaps. *Interconnect Planning*, 744 F.2d 1132, 1143 (Fed. Cir. 1985). Applicants believe that only through the exercise of impermissible hindsight have the cited references been selected and relied upon by the Office. Applicants respectfully submit that there is no teaching or suggestion in the cited art to motivate one of ordinary skill in the art to combine elements of the references to result in the presently claimed invention.

Applicants respectfully reiterate that the selecting an adjuvant for a particular vaccine is per se inventive and not routine experimentation or optimization.

The Examiner acknowledged that the review article by Sylvia van Drunen Littel-van den Hurk, Shawn L. Babiuk and Lorne A. Babiuk titled "Strategies for improved formulation and delivery of DNA vaccines to veterinary target species" published in Immunological Reviews

2004, Vol. 1999:113-125 ("Babiuk") summarizes the state of the art of DNA immunization. However, the Examiner believes that Babiuk, and the references cited therein, is not considered to be the state of the art at the time of filing. Applicants respectfully disagree and traverse the rejection.

Babiuk should be considered a reference supporting the Applicants' position of non-obviousness even though it is a post-filing date reference. See, e.g., MPEP 2164.05(a). "A later-dated reference provides evidence of what one skilled in the art would have known on or before the effective filing date of the patent application. *In re Hogan*, 559F.2d 595, 605, 194 USPQ 527, 537 (CCPA 1977). If individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993)". Even though this section of the MPEP deals with enablement, Applicants submit that a similar argument should be applied to the use of a post-filing reference, especially a review article, as indicia of non-obviousness.

The Examiner also alleges that Babiuk speaks of DNA vaccines in general and does not explicitly indicate that the specific bovine DNA vaccine of the '473 patent would not work in bovines. Contrary to the above assertion, Babiuk does not relate to the effectiveness of DNA vaccinination of bovine, but rather, relates to the state of the art regarding DNA immunization of bovines. Babiuk states that "[a]lthough the concept of DNA immunization has proven to be extremely successful in inducing immune responses in mice, significant barriers exists to effective induction of immunity in large animals and humans using DNA immununization. Indeed, there is not one DNA vaccine that has been approved for either human or veterinary use" (page 114, bottom of first column of Babiuk). Furthermore, Babiuk cautions that "[w]ith the exception of these reports [two studies where DMRIE-DOPE resulted in a stronger immune response in ponies and dogs--studies by the inventor Jean-Christophe Audonnet], there is a paucity of published information on the use of liposomes for DNA vaccines, specifically in large animals. Therefore it is difficult to assess the true efficacy of this approach." (page 115, bottom first column to top of second column of Babiuk) Therefore, Babiuk's statements remain

illustrating as a lack of reasonable expectation of success of DNA vaccination with liposomes in large animals.

In addition to the herein arguments and herewith literature, and the arguments of record, attention is respectfully directed to MPEP 2143.02 which provides that obviousness requires a reasonable expectation of success. As discussed herein and in the record, and through the literature herewith, there was no reasonable expectation of success of the instant invention prior to the present invention.

Accompanying this response is a Declaration by Dr. Lorne A. Babiuk, the senior author of Babiuk. According to the Declaration, there was a need in the art to improve the efficacy of DNA vaccination in bovines. The Declaration also states that there was no reasonable expectation of success that (a) methods that increased the efficacy of DNA vaccines in mice would extrapolate to bovines and (b) the cationic lipids of the present invention would improve the efficacy of a bovine DNA vaccine.

The Examiner is respectfully requested to consider and make of record the article by Serge Harpin, David J. Hurley, Majambu Mbikay, Brian Talbot and Youssef Elazhary titled "Vaccination of cattle with a DNA plasmid encoding the bovine viral diarrhoea virus major glycoprotein E2" published in the Journal of General Virology 1999, Vol. 80:3137-3144, hereinafter referred to as "Harpin", which is also cited on the accompanying Supplemental Information Disclosure Statement and PTO-1449.

The Examiner also dismisses the Applicants argument that if it would have been obvious to one of ordinary skill in the art to combine a DNA vaccine with a lipid, there would have been more than two studies discussed in Babiuk. The Examiner contends that the number of post filing studies that have been performed is inconsequential with respect to obviousness and the fact that at least two studies have been performed appears to support the Office's position of obviousness. While Applicants do not dispute that the number of post filing studies that have been performed is inconsequential with respect to obviousness, Applicants respectfully point out that the two studies discussed in Babiuk were conducted by Jean-Christophe Audonnet, an inventor of the present invention. Accordingly, the two studies were not performed by another, but by an inventor of the present invention.

The Examiner alleges that "Applicants appear to be arguing against DMRIE's ability to act as an adjuvant and to facilitate delivery of a therapeutic molecule". On the contrary, Applicants merely presented arguments that one of ordinary skill in the art does not recognize that all cationic lipids, such as DMRIE, are necessarily effective adjuvants. For example, as indicated in the '409 patent and the '131 patent, DMRIE was known to induce a low level of in vivo expression, a weak antibody response and no cytotoxic response. It is known to one of ordinary skill in the art that a vaccine needs to stimulate both humoral and cellular immunity to protect against a viral pathogen (an intracellular microorganism). The Examiner asserts that the '409 patent teaches "the adjuvant composition of the instant invention enhances the immune response of the vertebrate to the immunogen". The statement refers to the adjuvant of the '409 invention, i.e., GAP-DMORIE. According to the '409 patent, "[c]ationic lipids used previously for vaccination shows only low levels of humoral enhancement. GAP-DMORIE, in contrast to the prior art, is useful for enhancing the humoral response. Thus, the '409 patent admits that not all cationic lipids are recognized as effective adjuvants.

Furthermore, attention is respectfully directed to MPEP 2143 which mandates that the fact that references can be combined or modified is insufficient for an obviousness rejection; there must be some desirability in the art to modify reference teachings to arrive at an invention. In the present situation, as discussed herein and in the record, and through the literature herewith, there is no teaching, suggestion, incentive or motivation to modify the cited documents to arrive at the instant invention.

Accordingly, Applicants respectfully request the reconsideration and withdrawal of the double patenting rejections.

III. THE REJECTIONS UNDER 35 U.S.C. §103 ARE OVERCOME

Claims 84-91 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over claims 5-8 of the '473 patent in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Xiang et al. (Immunity 1995, 2:129-135), and Baker et al. (US Patent 5,106,733). Claims 84, 92, 94, 100 and 104 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over claims 5-8 of the '473 patent in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Li (WO 96/40945). Claims 84, 93, 97, 98 and 104 were rejected under 35 U.S.C.

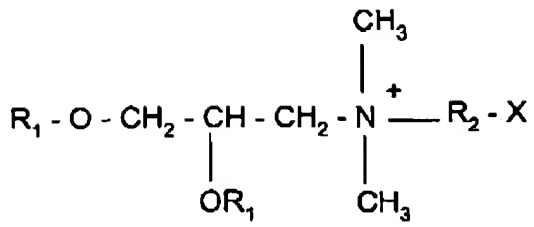
§103(a) as allegedly being unpatentable over claims 5-8 of the '473 patent in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Choi et al. (Virology 1998, 250:230-240). Claims 84- 118 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over claims 5-8 of the '473 patent in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Xiang et al. (Immunity 1995, 2:129-135), Baker et al. (US Patent 5,106,733), Li (WO 96/40945) and Choi et al. (Virology 1998, 250:230-240).

Claims 84, 92, 94, 95, 100 and 108 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over claims 5-8 of the '473 patent in view of the '409 patent and further in view of Li (WO 96/40945). Claims 84, 93, 97, 98 and 104 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over claims 5-8 of the '473 patent in view of the '409 patent and further in view of Choi et al. Claims 84-118 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over claims 5-8 of the '473 patent in view of the '409 patent and further in view of Xiang et al. (Immunity 1995, 2:129-135), Baker et al. (US Patent No. 5,106,733; 1992), Li (WO 96/40945) and Choi et al. (Virology 1998, 250:230-240).

These rejections are addressed collectively and are respectfully traversed.

While the applicants do not concede that the claims are obvious, this issue is moot as the '473 patent has been disqualified as prior art under 35 U.S.C. §103(c) as established by the concurrently filed Statement of Common Ownership. Therefore, the rejection under 103(a) over the '473 patent should be withdrawn. However, as stated above, Applicants respectfully request that the Examiner consider PCT Publication No. WO 98/03200, which was filed as Serial No. PCT/FR97/01325 on July 15, 1997. The PCT Publication was cited in the Supplemental Information Disclosure Statement filed November 3, 2004, and the Examiner made of record in the Office Action. The '473 patent is a continuation-in-part of International Application Serial No. PCT/FR97/01325 (the '01325 application). Applicants respectfully submit that the English text of the '473 patent is a translation of the '01325 application.

The present invention provides a DNA vaccine against a bovine pathogen comprising at least one plasmid that contains and expresses in a bovine host cell a nucleotide sequence encoding an immunogen of the bovine pathogen, wherein the bovine pathogen is BRSV, BVDV-1, BVDV-2 or bPI-3, and a cationic lipid containing a quaternary ammonium salt, of the formula



in which R_1 is a saturated or unsaturated linear aliphatic radical having 12 to 18 carbon atoms, R_2 is an aliphatic radical containing 2 or 3 carbon atoms, and X a hydroxyl or amine group.

The lipid can be DMRIE and the vaccine can further comprise DOPE. The vaccine can also further comprise bovine or porcine GM-CSF, or an expression vector that contains and expresses in a porcine host cell a nucleotide sequence encoding porcine GM-CSF, or an expression vector that contains and expresses in a bovine host cell a nucleotide sequence encoding porcine GM-CSF, wherein this additional expression vector can be a plasmid.

The nucleotide sequence encoding the immunogen can have deleted therefrom a portion encoding a transmembrane domain, and the plasmid can further contain and express in a a nucleotide sequence encoding a heterologous tPA signal sequence, such as a human tPA signal sequence. Even further, the plasmid can further contain a stabilizing intron, such as intron II of a rabbit beta-globin gene.

The Examiner is respectfully directed to the case law, namely, that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Further, as stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification." For the §103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988).

None of the cited documents teaches or suggests a DNA vaccine that comprises, *inter alia*, a plasmid that expresses DNA encoding an immunogen of a bovine pathogen, wherein the bovine pathogen is BRSV, BVDV-1, BVDV-2 or bPI-3. Neither Klavinskis nor the '409 patent

teach or suggest bovine pathogens of BRSV, BVDV-1, BVDV-2 or bPI-3. Xiang, Baker, Li and Choi do not cure the deficiencies of Klavinskis or the '409 patent. Accordingly, in view of the herein arguments and the accompanying reference, reconsideration and withdrawal of the 35 U.S.C. §103 rejection are respectfully requested.

As indicated above, selection of an adjuvant for a particular adjuvant for a particular vaccine is per se inventive and not routine experimentation or optimization. In summary, (a) there is no motivation to combine the cited references (b) the lipid adjuvants of Klavinskis and the '409 patent would not be expected to work in bovines or porcines and (c) one of ordinary skilled in the art would not use a cationic lipid (such as DMRIE) thought to induce a low level of expression, a weak antibody response and no cytotoxic response as an adjuvant.

The Examiner acknowledged that Example 17 of WO 01/5288 indicates that DMRIE-DOPE significantly enhances the neutralizing antibody response, but alleges that the superior result is suggested by the art of record and is not an unexpected result. However, the data remains significant because it illustrates the effectiveness of DMRIE-DOPE as an adjuvant, especially when, as described above, the '409 patent admits that not all cationic lipids are recognized as effective adjuvants. The data is also significant because it is contrary to the teachings of Harpin.

Accordingly, it is respectfully submitted that when one considers all of the teachings in the art, and the mandates of the case law and the MPEP, it is clear that the rejections cannot stand.

Therefore, the cited documents fail to teach or suggest the instant invention. Applicants reiterate that there is no motivation to combine the '473 patent with Klavinskis or the '409 patent. Xiang, Baker, Li and Choi do not cure the deficiencies of the '473 patent or the '409 patent. Accordingly, in view of the herein arguments and the accompanying references, reconsideration and withdrawal of the rejections under 35 U.S.C. § 103 are respectfully requested.